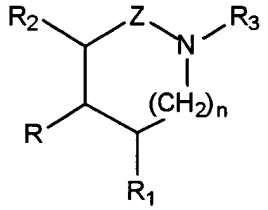
Amendments to the Claims

This listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of Claims:

1 (withdrawn). A compound of the formula:



wherein

Z is $-C(R_{18})(R_{19})-$ wherein R_{18} and R_{19} are hydrogen;

n is 0;

R is $-(CH_2)_m-W$ wherein m is 0 and W is $-C(O)_2-G$ wherein G is hydrogen;

R_1 and R_2 are independently selected from the group consisting of loweralkyl, alkenyl, alkynyl, alkoxyalkyl, alkoxycarbonylalkyl, hydroxyalkyl, haloalkyl, haloalkoxyalkyl, alkoxyalkoxyalkyl, thioalkoxyalkoxyalkyl, cycloalkyl, cycloalkylalkyl, aminocarbonylalkyl, alkylaminocarbonylalkyl, dialkylaminocarbonylalkyl, aminocarbonylalkenyl, alkylaminocarbonylalkenyl, dialkylaminocarbonylalkenyl, hydroxyalkenyl, aryl, arylalkyl, aryloxyalkyl, arylalkoxyalkyl, (N-alkanoyl-N-alkyl)aminoalkyl, alkylsulfonylamidoalkyl, heterocyclic, (heterocyclic)alkyl and $(R_{aa})(R_{bb})N-R_{cc}-$ wherein R_{aa} is aryl or arylalkyl, R_{bb} is hydrogen or alkanoyl and R_{cc} is alkylene; and

R_3 is $R_4-C(O)-R_5-$ wherein R_5 is alkylene and R_4 is selected from the group consisting of

(i) $(R_{11})(R_{12})N-$ wherein R_{11} is hydrogen and R_{12} is selected from the group

consisting of arylalkyl, and diarylalkyl

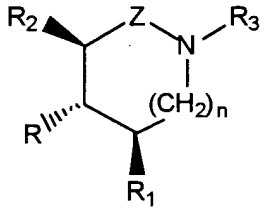
and

(ii) $(R_{11a})(R_{12a})N-N(H)-$ wherein R_{11a} and R_{12a} are independently

selected from the group consisting of aryl and alkyl;
or a pharmaceutically acceptable salt thereof.

2-20 (cancelled)

21 (withdrawn): The compound according to Claim 1 of the formula:



22-65 (cancelled)

66 (withdrawn): A method for antagonizing the action of endothelin comprising administering to a mammal in need of such treatment a therapeutically effective amount of a compound of Claim 1.

67 (withdrawn): A method for antagonizing the action of endothelin comprising administering to a mammal in need of such treatment a therapeutically effective amount of a compound of Claim 21.

68 (withdrawn): A method for antagonizing the action of endothelin comprising administering to a mammal in need of such treatment a therapeutically affective amount of *(2S,3R,4S)*-2-(2,2-Dimethylpentyl)-4-(7-methoxy-1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid.

69 (withdrawn): A method for antagonizing the action of endothelin comprising administering to a mammal in need of such treatment a therapeutically affective amount of *(2S,3R,4S)*-2-3-Fluoro-4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(2-(N-propyl-N-pentanesulfonyl)ethyl)-pyrrolidine-3-carboxylic acid.

70 (withdrawn): A method for treating hypertension, congestive heart failure, restenosis following arterial injury, renal failure, cancer, colitis, repurfusion injury, angina, pulmonary hypertension, migraine, cerebral or myocardial ischemia or atherosclerosis comprising administering to a mammal in need of such treatment a therapeutically effective amount of a compound of Claim 1.

71 (withdrawn): A method for treating coronary angina, cerebral vasospasm, acute and chronic renal failure, gastric ulceration, cyclosporin-induced nephrotoxicity, endotoxin-induced toxicity, asthma, LPL-related lipoprotein disorders, proliferative diseases, acute or chronic pulmonary hypertension, platelet aggregation, thrombosis, IL-2 mediated cardiotoxicity, nociception, colitis, vascular permeability disorders, ischemia-repurfusion injury, raynaud's disease and migraine comprising administering to a mammal in need of such treatment a therapeutically effective amount of a compound of claim 1.

72 (withdrawn): A method for treating hypertension, congestive heart failure, restenosis following arterial injury, renal failure, cancer, colitis, repurfusion injury, angina, pulmonary hypertension, migraine, cerebral or myocardial ischemia or atherosclerosis comprising administering to a mammal in need of such treatment a therapeutically effective amount of a compound of Claim 21.

73 (withdrawn): A method for treating hypertension, congestive heart failure, restenosis following arterial injury, renal failure, cancer, colitis, repurfursion injury, angina, pulmonary hypertension, migraine, cerebral or myocardial ischemia or atherosclerosis comprising administering to a mammal in need of such treatment a therapeutically effective amount of *(2S,3R,4S)*-2-(2,2-Dimethylpentyl)-4-(7-methoxy-1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid.

74 (withdrawn): A method for treating hypertension, congestive heart failure, restenosis following arterial injury, renal failure, cancer, colitis, repurfursion injury, angina, pulmonary hypertension, migraine, cerebral or myocardial ischemia or atherosclerosis comprising administering to a mammal in need of such treatment a therapeutically effective amount of *(2S,3R,4S)*-2-3-Fluoro-4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(2-(N-propyl-N-pentanesulfonyl)ethyl)-pyrrolidine-3-carboxylic acid.

75 (withdrawn): A method for treating coronary angina, cerebral vasospasm, acute and chronic renal failure, gastric ulceration, cyclosporin-induced nephrotoxicity, endotoxin-induced toxicity, asthma, LPL-related lipoprotein disorders, proliferative diseases, acute or chronic pulmonary hypertension, platelet aggregation, thrombosis, IL-2 mediated cardiotoxicity, nociception, colitis, vascular permeability disorders, ischemia-repurfusion injury, raynaud's disease and migraine comprising administering to a mammal in need of such treatment a therapeutically effective amount of a compound of claim 21.

76 (withdrawn): A method for treating coronary angina, cerebral vasospasm, acute and chronic renal failure, gastric ulceration, cyclosporin-induced nephrotoxocity, endotoxin-induced toxicity, asthma, LPL-related lipoprotein disorders, proliferative diseases, acute or chronic pulmonary hypertension, platelet aggregation, thrombosis, IL-2 mediated cardiotoxicity, nociception, colitis, vascular permeability disorders, ischemia-repurfusion injury,

raynaud's disease and migraine comprising administering to a mammal in need of such treatment a therapeutically effective amount of a compound of *(2S,3R,4S)*-2-(2,2-Dimethylpentyl)-4-(7-methoxy-1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid.

77 (withdrawn): A method for treating coronary angina, cerebral vasospasm, acute and chronic renal failure, gastric ulceration, cyclosporin-induced nephrotoxocity, endotoxin-induced toxicity, asthma, LPL-related lipoprotein disorders, proliferative diseases, acute or chronic pulmonary hypertension, platelet aggregation, thrombosis, IL-2 mediated cardiotoxicity, nociception, colitis, vascular permeability disorders, ischemia-repurfusion injury, raynaud's disease and migraine comprising administering to a mammal in need of such treatment a therapeutically effective amount of a compound of *(2S,3R,4S)*-2-3-Fluoro-4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(2-(N-propyl-N-pentanesulfonyl)ethyl)-pyrrolidine-3-carboxylic acid.

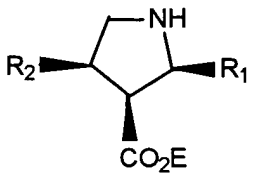
78 (withdrawn): A method for treating treating hypertension, congestive heart failure, restenosis following arterial injury, cerebral or myocardial ischemia or atherosclerosis comprising administering to a mammal in need of such treatment a therapeutically effective amount of a compound of Claim 1 in combination with one or more cardiovascular agents.

79 (withdrawn): A method for treating treating hypertension, congestive heart failure, cerebral or myocardial ischemia or atherosclerosis comprising administering to a mammal in need of such treatment a therapeutically effective amount of a compound of Claim 21 in combination with one or more cardiovascular agents.

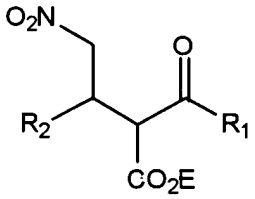
80 (withdrawn): A method for treating treating hypertension, congestive heart failure, cerebral or myocardial ischemia or atherosclerosis comprising

administering to a mammal in need of such treatment a therapeutically effective amount of a compound of *(2S,3R,4S)*-2-(2,2-Dimethylpentyl)-4-(7-methoxy-1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid in combination with one or more cardiovascular agents.

81 (withdrawn): A process for the preparation of a compound of the formula:



wherein E is a carboxy-protecting group and R_1 and R_2 are independently selected from loweralkyl, alkoxyalkyl, alkoxycarbonylalkyl, hydroxyalkyl, haloalkyl, haloalkoxyalkyl, alkoxyalkoxyalkyl, thioalkoxyalkoxyalkyl, cycloalkyl, cycloalkylalkyl, aminocarbonylalkyl, alkylaminocarbonylalkyl, dialkylaminocarbonylalkyl, aminocarbonylalkenyl, alkylaminocarbonylalkenyl, dialkylaminocarbonylalkenyl, aryl, arylalkyl, aryloxyalkyl, arylalkoxyalkyl, (N-alkanoyl-N-alkyl)aminoalkyl, alkylsulfonylamidoalkyl, heterocyclic and (heterocyclic)alkyl; or a salt thereof, comprising a) catalytic hydrogenation of a compound of the formula:



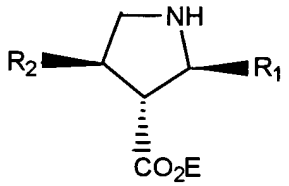
wherein E, R_1 and R_2 are defined as above and b) catalytic hydrogenation of the product of step a) in the presence of an acid or a mixture of acids.

82 (withdrawn): The process of Claim 71 wherein E is loweralkyl, R_1 is aryl and R_2 is heterocyclic.

83 (withdrawn): The process of Claim 71 wherein the hydrogenation catalyst is Raney nickel and the acid is a mixture of acetic acid and trifluoroacetic acid.

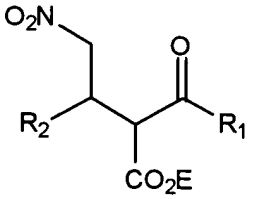
84 (withdrawn): The process of Claim 71 wherein E is loweralkyl, R_1 is 4-methoxyphenyl and R_2 is 1,3-benzodioxol-5-yl.

85 (withdrawn): A process for the preparation of a compound of the formula:



wherein E is a carboxy-protecting group and R_1 and R_2 are independently selected from loweralkyl, alkoxyalkyl, alkoxycarbonylalkyl, hydroxyalkyl, haloalkyl, haloalkoxyalkyl, alkoxyalkoxyalkyl, thioalkoxyalkoxyalkyl, cycloalkyl, cycloalkylalkyl, aminocarbonylalkyl, alkylaminocarbonylalkyl, dialkylaminocarbonylalkyl, aminocarbonylalkenyl, alkylaminocarbonylalkenyl, dialkylaminocarbonylalkenyl, aryl, arylalkyl, aryloxyalkyl, arylalkoxyalkyl, (N-alkanoyl-N-alkyl)aminoalkyl, alkylsulfonylamidoalkyl, heterocyclic and (heterocyclic)alkyl; or a salt thereof, comprising

a) catalytic hydrogenation of a compound of the formula:



wherein E, R_1 and R_2 are defined as above,

b) catalytic hydrogenation of the product of step a) in the presence of an acid or a mixture of acids, and

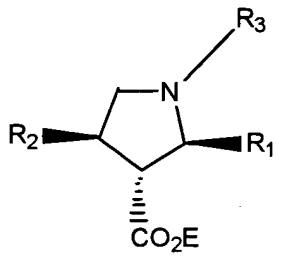
c) epimerization of the product of step b) with a base.

86 (withdrawn): The process of Claim 75 wherein E is loweralkyl, R_1 is aryl and R_2 is heterocyclic.

87 (withdrawn): The process of Claim 75 wherein the hydrogenation catalyst is Raney nickel and the acid is a mixture of acetic acid and trifluoroacetic acid.

88 (withdrawn): The process of Claim 75 wherein E is loweralkyl, R_1 is 4-methoxyphenyl and R_2 is 1,3-benzodioxol-5-yl.

89 (withdrawn): A process for the preparation of a compound of the formula:



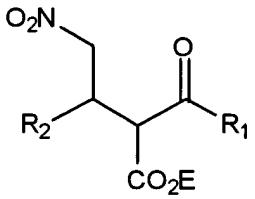
wherein E is a carboxy-protecting group, R_1 and R_2 are independently selected from loweralkyl, alkoxyalkyl, alkoxycarbonylalkyl, hydroxyalkyl, haloalkyl, haloalkoxyalkyl, alkoxyalkoxyalkyl, thioalkoxyalkoxyalkyl, cycloalkyl, cycloalkylalkyl, aminocarbonylalkyl, alkylaminocarbonylalkyl, dialkylaminocarbonylalkyl, aminocarbonylalkenyl, alkylaminocarbonylalkenyl, dialkylaminocarbonylalkenyl, aryl, arylalkyl, aryloxyalkyl, arylalkoxyalkyl, (N-alkanoyl-N-alkyl)aminoalkyl, alkylsulfonylamidoalkyl, heterocyclic and (heterocyclic)alkyl and R_3 is R_4-C(O)-R_5- wherein R_5 is alkylene and R_4 is $(R_{11})(R_{12})$N- wherein R_{11} and R_{12} are independently selected from

(1) loweralkyl,
(2) haloalkyl,
(3) alkoxyalkyl,

(4) haloalkoxyalkyl,
(5) alkenyl,
(6) alkynyl,
(7) cycloalkyl,
(8) cycloalkylalkyl,
(9) aryl,
(10) heterocyclic,
(11) arylalkyl and
(12) (heterocyclic)alkyl;
(13) hydroxyalkyl,
(14) alkoxy,
(15) aminoalkyl, and
(16) trialkylaminoalkyl,

or a salt thereof, comprising

a) catalytic hydrogenation of a compound of the formula:



wherein E, R_1 and R_2 are defined as above,

b) catalytic hydrogenation of the product of step a) in the presence of an acid or a mixture of acids,

c) epimerization of the product of step b) with a base and

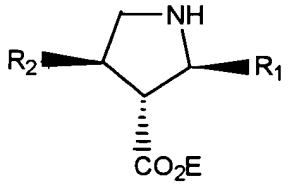
d) alkyation of the product of step c) with a compound of the formula R_3-X wherein X is a leaving group and R_3 is defined as above.

90 (withdrawn): The process of Claim 79 wherein E is loweralkyl, R_1 is aryl, R_2 is heterocyclic and R_3 is $-CH_2C(O)NR_{11}R_{12}$ wherein R_{11} and R_{12} are independently selected from the group consisting of loweralkyl.

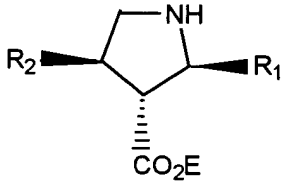
91 (withdrawn): The process of Claim 79 wherein the hydrogenation catalyst is Raney nickel and the acid is a mixture of acetic acid and trifluoroacetic acid.

92 (withdrawn): The process of Claim 79 wherein E is loweralkyl, R_1 is 4-methoxyphenyl, R_2 is 1,3-benzodioxol-5-yl, R_3 is $-CH_2C(O)N(n\text{-}Bu)_2$ and X is a halogen or sulfonate leaving group.

93 (withdrawn): A process for the preparation of the substantially pure (+)-trans,trans optical isomer of the compound of the formula:



wherein E is loweralkyl, R_1 is 4-methoxyphenyl and R_2 is 1,3-benzodioxol-5-yl, or a salt thereof, comprising reacting a mixture of the (+) and (-) enantiomers of the compound of the formula:



wherein E is loweralkyl, R_1 is 4-methoxyphenyl and R_2 is 1,3-benzodioxol-5-yl with S-(+)- mandelic acid and separating the mandelate salt of the (+)-trans,trans optical isomer.

94-95 (cancelled)

96 (withdrawn): A method for treating hypertension, congestive heart failure, restenosis following arterial injury, renal failure, cancer, colitis,

repurfusion injury, angina, pulmonary hypertension, migraine, cerebral or mycocardial ischemia, atherosclerosis, coronary angina, cerebral vasospasm, acute and chronic renal failure, gastric ulceration, cyclosporin-induced nephrotoxocity, endotoxin-induced toxicity, asthma, LPL-related lipoprotein disorders, proliferative diseases, acute or chronic pulmonary hypertension, platelet aggregation, thrombosis, IL-2 mediated cardiotoxicity, nociception, colitis, vascular permeability disorders, ischemia-repurfusion injury, Raynaud's disease, prostatic hyperplasia, and migraine comprising a therapeutically effective amount of a compound of claim 94, wherein said compound has an attached charged functionality which reduces the degree of plasma protein binding of the compound.

97 (withdrawn): A method of improving the in vivo activity of compounds by reducing the amount of compound bound to protein by attaching a charged functionality to the compound.

98 (withdrawn): A method of claim 97 wherein the charged functionality carries a positive charge at physiological pH.

99 (withdrawn): A method for inhibiting bone metastases and metastatic growth in a patient which comprises administering to the patient in need thereof a therapeutically effective amount of an endothelin ET-A receptor antagonist.

100 (withdrawn): The method of Claim 99 wherein the bone metastases are osteoblastic.

101 (withdrawn): The method of Claim 100 wherein the osteoblastic bone metastases result from the spread of a primary cancer selected from breast,

prostate, lung, kidney, thyroid, myeloma, lymphoma, sarcoma, osteosarcoma, and ovarian.

102 (withdrawn): The method of Claim 101 wherein the primary cancer is prostate cancer and the patient is male.

103 (withdrawn): The method of Claim 99 which additionally comprises co-administeration of an anticancer drug.

104 (withdrawn): The method of Claim 101 wherein the anticancer drug agent is selected from leuprolide, goserelin, bicalutamide, nilutamide, flutamide, vitamin D, vitamin D analogues, estrogen, estrogen analogues, prednisone, hydrocortisone, ketoconazole, cyproterone acetate, and progesterone.

105 (withdrawn): The method of Claim 99 which additionally comprises the administeration of radiation therapy.

106 (withdrawn): The method of Claim 99 which additionally comprises the administeration of at least one therapeutic agent which impedes net bone loss.

107 (withdrawn): The method of Claim 106 wherein the therapeutic agent is a bisphosphonate.

108 (withdrawn): The method of Claim 99 wherein the endothelin antagonist is an ET_A-selective endothelin antagonist.

109 (withdrawn): A method for the inhibition of bone loss in a patient which comprises administering to the patient in need thereof a therapeutically effective amount of an endothelin ET-A receptor antagonist.

110 (withdrawn): The method of Claim 109 wherein the patient has cancer.

111 (withdrawn): The method of Claim 109 wherein the cancer is prostate cancer and the patient is male.

112 (withdrawn): The method of Claim 109 which additionally comprises the administeration of at least one therapeutic agent which impedes net bone loss.

113 (withdrawn): The method of Claim 112 wherein the therapeutic agent is a bisphosphonate.

114 (withdrawn): A method for the reduction of cancer-related pain in a patient which comprises administering to the patient in need thereof a therapeutically effective amount of an endothelin ET-A receptor antagonist.

115 (withdrawn): The method of Claim 1614 wherein the cancer is prostate cancer and the patient is male.

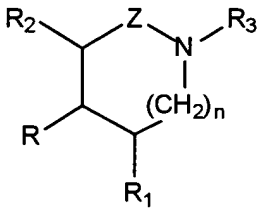
116 (withdrawn): The method of Claim 114 which additionally comprises

the administeration of an anticancer drug.

117 (withdrawn): The method of Claim 116 wherein the anticancer drug is selected from leuprolide, goserelin, bicalutamide, nilutamide, flutamide, vitamin D, vitamin D analogues, estrogen, estrogen analogues, prednisone, hydrocortisone, ketoconazole, cyproterone acetate, and progesterone.

118 (withdrawn): The method of Claim 115 which additionally comprises the administeration of radiation therapy.

119 (withdrawn): A method for inhibiting bone metastases in a patient which comprises administering to the patient in need thereof a therapeutically effective amount of a compound of formula I:



I

wherein

R is $-(CH_2)_m-W$;

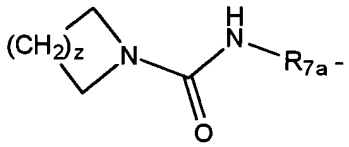
Z is selected from $-C(R_{18})(R_{19})-$ and -C(O)-;

R_1 and R_2 are independently selected from hydrogen, loweralkyl, alkenyl, alkynyl, alkoxyalkyl, alkoxycarbonylalkyl, hydroxyalkyl, haloalkyl, haloalkoxyalkyl, alkoxyalkoxyalkyl, thioalkoxyalkoxyalkyl, cycloalkyl, cycloalkylalkyl, aminocarbonylalkyl, alkylaminocarbonylalkyl, dialkylaminocarbonylalkyl, aminocarbonylalkenyl, alkylaminocarbonylalkenyl, dialkylaminocarbonylalkenyl, hydroxyalkenyl, aryl, arylalkyl, aryloxyalkyl, arylalkoxyalkyl, (N-alkanoyl-N-alkyl)aminoalkyl, alkylsulfonylamidoalkyl, heterocyclic, (heterocyclic)alkyl, and $(R_{aa})(R_{bb})N-R_{cc}-$,

with the proviso that one or both of R_1 and R_2 is other than hydrogen;

R_3 is selected from R_4-C(O)-R_5-, R_4-R_{5a}-, R_4-C(O)-R_5-N(R_6)-, R_6-$S(O)_2$-R_7- R_{26}-S(O)-R_{27}-, R_{22}-O-C(O)-R_{23}-, loweralkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, aryloxyalkyl, heterocyclic, (heterocyclic)alkyl, alkoxyalkyl, alkoxyalkoxyalkyl, and R_{13}-C(O)-CH(R_{14})-;

R_4 and R_6 are independently selected from (R_{11})(R_{12})N-, loweralkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heterocyclic, (heterocyclic)alkyl, alkoxyalkyl, hydroxyalkyl, haloalkyl, haloalkenyl, haloalkoxyalkyl, haloalkoxy, alkoxyhaloalkyl, alkylaminoalkyl, dialkylaminoalkyl, alkoxy, and



R_5 is selected from a covalent bond, alkylene, alkenylene, -N(R_{20})-R_8-, -R_{8a}-N(R_{20})-R_8-, -O-R_9-, and
-R_{9a}-O-R_9-;

R_6 is selected from loweralkyl, haloalkyl, alkoxyalkyl, haloalkoxyalkyl, aryl or arylalkyl;

R_7 is a covalent bond, alkylene, alkenylene -N(R_{21})-R_{10}-, and -R_{10a}-N(R_{21})-R_{10}-;

R_8 is selected from alkylene and alkenylene;

R_9 is alkylene;

R_{10} is selected from alkylene and alkenylene;

R_{11} and R_{12} are independently selected from hydrogen, loweralkyl, haloalkyl, alkoxyalkyl, haloalkoxyalkylalkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, aryl, heterocyclic, arylalkyl, (heterocyclic)alkyl, hydroxyalkyl, alkoxy, aminoalkyl,trialkylaminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, and carboxyalkyl;

R_{13} is selected from amino, alkylamino and dialkylamino;

R_{14} is selected from aryl and R_{15}-C(O)-;

R_{15} is selected from amino, alkylamino and dialkylamino;

R_{16} is selected from loweralkyl, haloalkyl, aryl and dialkylamino;

R_{17} is loweralkyl;

R_{18} and R_{19} are independently selected from hydrogen and loweralkyl;

R_{20} is selected from hydrogen, loweralkyl, alkenyl, haloalkyl, alkoxyalkyl, haloalkoxyalkyl, cylcoalkyl and cycloalkylalkyl;

R_{21} is selected from hydrogen, loweralkyl, alkenyl, haloalkyl, alkoxyalkyl, haloalkoxyalkyl, aryl and arylalkyl;

R_{22} is selected from a carboxy protecting group and heterocyclic;

R_{23} is selected from covalent bond, alkylene, alkenylene and -N(R_{24})-R_{25}-;

R_{24} is selected from hydrogen and loweralkyl;

R_{25} is alkylene;

R_{26} is selected from loweralkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heterocyclic, (heterocyclic)alkyl, alkoxyalkyl and alkoxy-substituted haloalkyl;

R_{27} is selected from alkylene and alkenylene;

R_{5a} is selected from alkylene and alkenylene;

R_{7a} is alkylene;

R_{8a} is selected from alkylene and alkenylene;

R_{9a} is alkylene;

R_{10a} is selected from alkylene and alkenylene;

R_{aa} is selected from aryl and arylalkyl;

R_{bb} is selected from hydrogen and alkanoyl;

R_{cc} is alkylene;

m is 0-6;

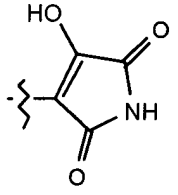
n is 0 or 1;

z is 0-5;

E is selected from hydrogen, loweralkyl and arylalkyl;

G is selected from hydrogen and a carboxy protecting group; and

W is selected from -$C(O)_2$-G; -PO_3H_2, -P(O)(OH)(E), -CN, -$C(O)NHR_{17}$, alkylaminocarbonyl, dialkylaminocarbonyl, tetrazolyl, hydroxy, alkoxy, sulfonamido, -$C(O)NHS(O)_2R_{16}$, -$S(O)_2NHC(O)R_{16}$,



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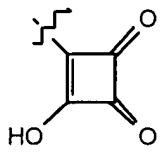

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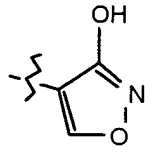

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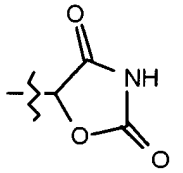

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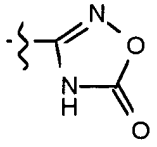

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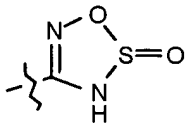

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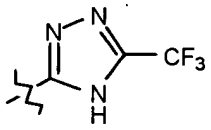
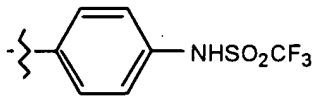


, and


,
or a pharmaceutically acceptable salt thereof.

120 (withdrawn): The method of Claim 119 wherein the bone metastases are osteoblastic.

121 (withdrawn): The method of Claim 120 wherein the osteoblastic bone metastases result from the spread of a primary cancer selected from breast, prostate, lung, kidney, thyroid, myeloma, lymphoma, sarcoma, osteosarcoma, and ovarian.

122 (withdrawn): The method of Claim 121 wherein the primary cancer is prostate cancer and the patient is male.

123 (withdrawn): The method of Claim 119 which additionally comprises the administeration of an anticancer drug.

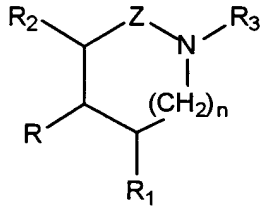
124 (withdrawn): The method of Claim 123 wherein the additional anticancer drug is selected from leuprolide, goserelin, bicalutamide, nilutamide, flutamide, vitamin D, vitamin D analogues, estrogen, estrogen analogues, prednisone, hydrocortisone, ketoconazole, cyproterone acetate, and progesterone.

125 (withdrawn): The method of Claim 119 which additionally comprises the administeration of radiation therapy.

126 (withdrawn): The method of Claim 119 which additionally comprises the administeration of at least one therapeutic agent which impedes net bone loss.

127 (withdrawn): The method of Claim 126 wherein the therapeutic agent is a bisphosphonate.

128 (withdrawn): A method for the inhibition of bone loss in cancer patients which comprises administering to the patient in need thereof a therapeutically effective amount of a compound of formula I:



I

wherein

R is $-(CH_2)_m-W$;

Z is selected from $-C(R_{18})(R_{19})-$ and $-C(O)-$;

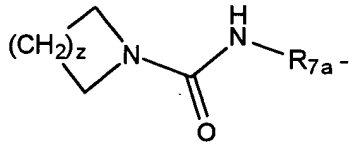
R_1 and R_2 are independently selected from hydrogen, loweralkyl, alkenyl, alkynyl, alkoxyalkyl, alkoxycarbonylalkyl, hydroxyalkyl, haloalkyl, haloalkoxyalkyl, alkoxyalkoxyalkyl, thioalkoxyalkoxyalkyl, cycloalkyl, cycloalkylalkyl, aminocarbonylalkyl, alkylaminocarbonylalkyl, dialkylaminocarbonylalkyl, aminocarbonylalkenyl, alkylaminocarbonylalkenyl, dialkylaminocarbonylalkenyl, hydroxyalkenyl, aryl, arylalkyl, aryloxyalkyl, arylalkoxyalkyl, (N-alkanoyl-N-alkyl)aminoalkyl, alkylsulfonylamidoalkyl, heterocyclic, (heterocyclic)alkyl, and $(R_{aa})(R_{bb})N-R_{cc}-$,

with the proviso that one or both of R_1 and R_2 is other than hydrogen;

R_3 is selected from $R_4-C(O)-R_5-$, $R_4-R_{5a}-$, $R_4-C(O)-R_5-N(R_6)-$, $R_6-S(O)_2-R_7-$ $R_{26}-S(O)-R_{27}-$, $R_{22}-O-C(O)-R_{23}-$, loweralkyl, alkenyl, alkynyl,

cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, aryloxyalkyl, heterocyclic, (heterocyclic)alkyl, alkoxyalkyl, alkoxyalkoxyalkyl, and R_{13}-C(O)-CH(R_{14})-;

R_4 and R_6 are independently selected from (R_{11})(R_{12})N-, loweralkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heterocyclic, (heterocyclic)alkyl, alkoxyalkyl, hydroxyalkyl, haloalkyl, haloalkenyl, haloalkoxyalkyl, haloalkoxy, alkoxyhaloalkyl, alkylaminoalkyl, dialkylaminoalkyl, alkoxy, and



R_5 is selected from a covalent bond, alkylene, alkenylene, -N(R_{20})-R_8-, -R_{8a}-N(R_{20})-R_8-, -O-R_9-, and
-R_{9a}-O-R_9-;

R_6 is selected from loweralkyl, haloalkyl, alkoxyalkyl, haloalkoxyalkyl, aryl or arylalkyl;

R_7 is a covalent bond, alkylene, alkenylene -N(R_{21})-R_{10}-, and -R_{10a}-N(R_{21})-R_{10}-;

R_8 is selected from alkylene and alkenylene;

R_9 is alkylene;

R_{10} is selected from alkylene and alkenylene;

R_{11} and R_{12} are independently selected from hydrogen, loweralkyl, haloalkyl, alkoxyalkyl, haloalkoxyalkylalkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, aryl, heterocyclic, arylalkyl, (heterocyclic)alkyl, hydroxyalkyl, alkoxy, aminoalkyl,trialkylaminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, and carboxyalkyl;

R_{13} is selected from amino, alkylamino and dialkylamino;

R_{14} is selected from aryl and R_{15}-C(O)-;

R_{15} is selected from amino, alkylamino and dialkylamino;

R_{16} is selected from loweralkyl, haloalkyl, aryl and dialkylamino;

R_{17} is loweralkyl;

R_{18} and R_{19} are independently selected from hydrogen and loweralkyl;

R_{20} is selected from hydrogen, loweralkyl, alkenyl, haloalkyl, alkoxyalkyl, haloalkoxyalkyl, cylcoalkyl and cycloalkylalkyl;

R_{21} is selected from hydrogen, loweralkyl, alkenyl, haloalkyl, alkoxyalkyl, haloalkoxyalkyl, aryl and arylalkyl;

R_{22} is selected from a carboxy protecting group and heterocyclic;

R_{23} is selected from covalent bond, alkylene, alkenylene and -N(R_{24})-R_{25}-;

R_{24} is selected from hydrogen and loweralkyl;

R_{25} is alkylene;

R_{26} is selected from loweralkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heterocyclic, (heterocyclic)alkyl, alkoxyalkyl and alkoxy-substituted haloalkyl;

R_{27} is selected from alkylene and alkenylene;

R_{5a} is selected from alkylene and alkenylene;

R_{7a} is alkylene;

R_{8a} is selected from alkylene and alkenylene;

R_{9a} is alkylene;

R_{10a} is selected from alkylene and alkenylene;

R_{aa} is selected from aryl and arylalkyl;

R_{bb} is selected from hydrogen and alkanoyl;

R_{cc} is alkylene;

m is 0-6;

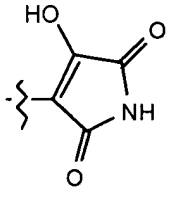
n is 0 or 1;

z is 0-5;

E is selected from hydrogen, loweralkyl and arylalkyl;

G is selected from hydrogen and a carboxy protecting group; and

W is selected from -C(O)$_2$-G; -PO_3H_2, -P(O)(OH)(E), -CN, -C(O)NHR_{17}, alkylaminocarbonyl, dialkylaminocarbonyl, tetrazolyl, hydroxy, alkoxy, sulfonamido, -C(O)NHS(O)$_2R_{16}$, -S(O)$_2$NHC(O)R_{16},



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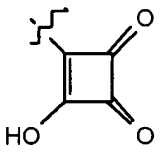

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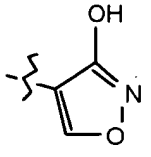

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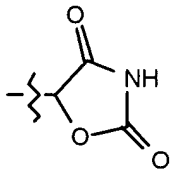

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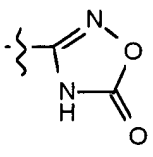

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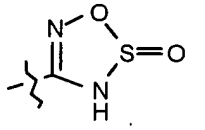
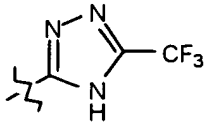
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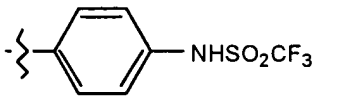

,

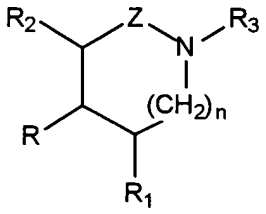
or a pharmaceutically acceptable salt thereof.

129 (withdrawn): The method of Claim 128 wherein the cancer is prostate cancer and the patient is male.

130 (withdrawn): The method of Claim 128 which additionally comprises the administeration of at least one therapeutic agent which impedes net bone loss.

131 (withdrawn): The method of Claim 130 wherein the therapeutic agent is a bisphosphonate.

132 (withdrawn): A method for the reduction of cancer-related pain which comprises administering to a patient in need thereof a therapeutically effective amount of a compound of formula I:



I

wherein

R is $-(CH_2)_m-W$;

Z is selected from $-C(R_{18})(R_{19})-$ and $-C(O)-$;

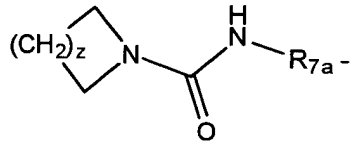
R_1 and R_2 are independently selected from hydrogen, loweralkyl, alkenyl, alkynyl, alkoxyalkyl, alkoxycarbonylalkyl, hydroxyalkyl, haloalkyl, haloalkoxyalkyl, alkoxyalkoxyalkyl, thioalkoxyalkoxyalkyl, cycloalkyl,

cycloalkylalkyl, aminocarbonylalkyl, alkylaminocarbonylalkyl, dialkylaminocarbonylalkyl, aminocarbonylalkenyl, alkylaminocarbonylalkenyl, dialkylaminocarbonylalkenyl, hydroxyalkenyl, aryl, arylalkyl, aryloxyalkyl, arylalkoxyalkyl, (N-alkanoyl-N-alkyl)aminoalkyl, alkylsulfonylamidoalkyl, heterocyclic, (heterocyclic)alkyl, and $(R_{aa})(R_{bb})N\text{-}R_{cc}$-,

with the proviso that one or both of R_1 and R_2 is other than hydrogen;

R_3 is selected from R_4-C(O)-R_5-, R_4-R_{5a}-, R_4-C(O)-R_5-N(R_6)-, R_6-$S(O)_2$-R_7- R_{26}-S(O)-R_{27}-, R_{22}-O-C(O)-R_{23}-, loweralkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, aryloxyalkyl, heterocyclic, (heterocyclic)alkyl, alkoxyalkyl, alkoxyalkoxyalkyl, and R_{13}-C(O)-CH(R_{14})-;

R_4 and R_6 are independently selected from $(R_{11})(R_{12})N$-, loweralkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heterocyclic, (heterocyclic)alkyl, alkoxyalkyl, hydroxyalkyl, haloalkyl, haloalkenyl, haloalkoxyalkyl, haloalkoxy, alkoxyhaloalkyl, alkylaminoalkyl, dialkylaminoalkyl, alkoxy, and



R_5 is selected from a covalent bond, alkylene, alkenylene, -N(R_{20})-R_8-, -R_{8a}-N(R_{20})-R_8-, -O-R_9-, and
-R_{9a}-O-R_9-;

R_6 is selected from loweralkyl, haloalkyl, alkoxyalkyl, haloalkoxyalkyl, aryl or arylalkyl;

R_7 is a covalent bond, alkylene, alkenylene -N(R_{21})-R_{10}-, and -R_{10a}-N(R_{21})-R_{10}-;

R_8 is selected from alkylene and alkenylene;

R_9 is alkylene;

R_{10} is selected from alkylene and alkenylene;

R_{11} and R_{12} are independently selected from hydrogen, loweralkyl, haloalkyl, alkoxyalkyl, haloalkoxyalkylalkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, aryl, heterocyclic, arylalkyl, (heterocyclic)alkyl, hydroxyalkyl, alkoxy, aminoalkyl,trialkylaminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, and carboxyalkyl;

R_{13} is selected from amino, alkylamino and dialkylamino;

R_{14} is selected from aryl and R_{15}-C(O)-;

R_{15} is selected from amino, alkylamino and dialkylamino;

R_{16} is selected from loweralkyl, haloalkyl, aryl and dialkylamino;

R_{17} is loweralkyl;

R_{18} and R_{19} are independently selected from hydrogen and loweralkyl;

R_{20} is selected from hydrogen, loweralkyl, alkenyl, haloalkyl, alkoxyalkyl, haloalkoxyalkyl, cylcoalkyl and cycloalkylalkyl;

R_{21} is selected from hydrogen, loweralkyl, alkenyl, haloalkyl, alkoxyalkyl, haloalkoxyalkyl, aryl and arylalkyl;

R_{22} is selected from a carboxy protecting group and heterocyclic;

R_{23} is selected from covalent bond, alkylene, alkenylene and -N(R_{24})-R_{25}-;

R_{24} is selected from hydrogen and loweralkyl;

R_{25} is alkylene;

R_{26} is selected from loweralkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heterocyclic, (heterocyclic)alkyl, alkoxyalkyl and alkoxy-substituted haloalkyl;

R_{27} is selected from alkylene and alkenylene;

R_{5a} is selected from alkylene and alkenylene;

R_{7a} is alkylene;

R_{8a} is selected from alkylene and alkenylene;

R_{9a} is alkylene;

R_{10a} is selected from alkylene and alkenylene;

R_{aa} is selected from aryl and arylalkyl;

R_{bb} is selected from hydrogen and alkanoyl;

R_{cc} is alkylene;

m is 0-6;

n is 0 or 1;

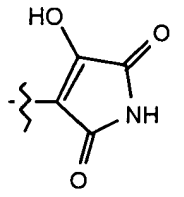
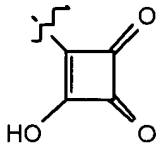
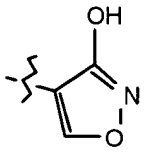
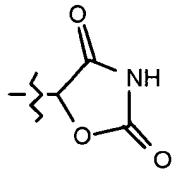
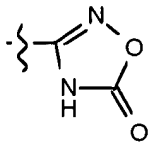
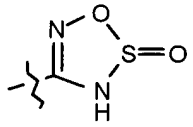
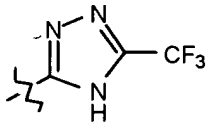
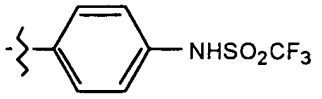
z is 0-5;

E is selected from hydrogen, loweralkyl and arylalkyl;

G is selected from hydrogen and a carboxy protecting group; and

W is selected from -$C(O)_2$-G; -PO_3H_2, -P(O)(OH)(E),

-CN, -C(O)NHR17, alkylaminocarbonyl, dialkylaminocarbonyl, tetrazolyl, hydroxy, alkoxy, sulfonamido, -C(O)NHS(O)2R16, -S(O)2NHC(O)R16,









, and

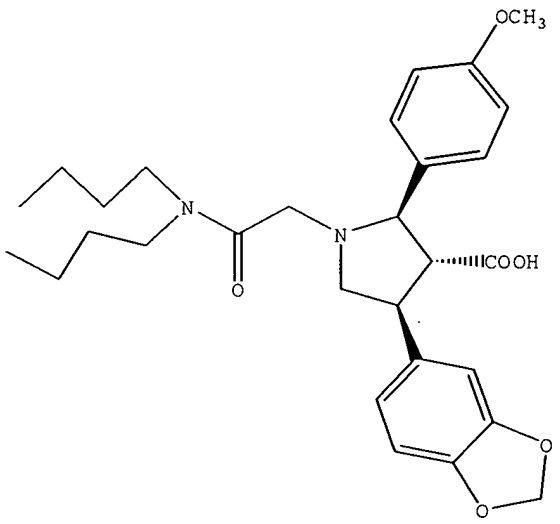
or a pharmaceutically acceptable salt thereof.

133 (withdrawn): The method of Claim 132 wherein the cancer is prostate cancer and the patient is male.

134 (withdrawn): The method of Claim 132 which additionally comprises the administeration of an anticancer drug.

135 (withdrawn): The method of Claim 134 wherein the additional anticancer drug is selected from leuprolide, goserelin, bicalutamide, nilutamide, flutamide, vitamin D, vitamin D analogues, estrogen, estrogen analogues, prednisone, hydrocortisone, ketoconazole, cyproterone acetate, and progesterone.

136 (withdrawn): A method for inhibiting bone metastases in a patient which comprises administering to the patient in need thereof a therapeutically effective amount of a compound of formula III



III.

39 137 (withdrawn): The method of Claim 136 wherein the bone metastases are osteoblastic.

138 (withdrawn): The method of Claim 137 wherein the osteoblastic bone metastases result from the spread of a primary cancer selected from breast, prostate, lung, kidney, thyroid, myeloma, lymphoma, sarcoma, osteosarcoma, and ovarian.

139 (withdrawn): The method of Claim 138 wherein the primary cancer is prostate cancer and the patient is male.

140 (withdrawn): The method of Claim 138 which additionally comprises the administeration of an anticancer drug.

141 (withdrawn): The method of Claim 138 wherein the additional anticancer drug is selected from leuprolide, goserelin, bicalutamide, nilutamide, flutamide, vitamin D, vitamin D analogues, estrogen, estrogen analogues, prednisone, hydrocortisone, ketoconazole, cyproterone acetate, and

progesterone.

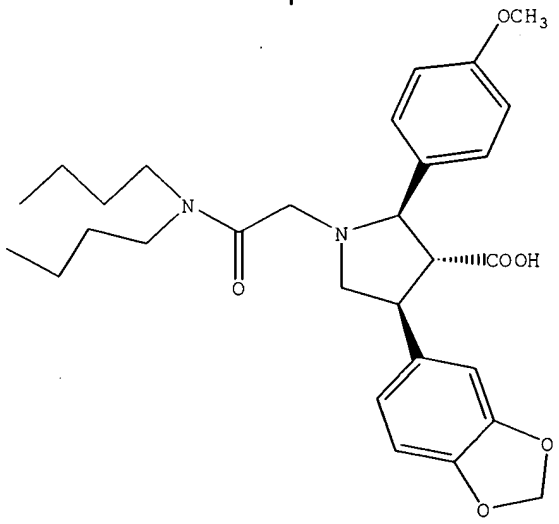
142 (withdrawn): The method of Claim 138 which additionally comprises the administeration of radiation therapy.

143 (withdrawn): The method of Claim 138 which additionally comprises the administeration of at least one therapeutic agent which impedes net bone loss.

144 (withdrawn): The method of Claim 143 wherein the agent is a bisphosphonate.

145 (withdrawn): The method of Claim 138 wherein the endothelin antagonist is an ET_A-selective endothelin antagonist.

146 (withdrawn): A method for the inhibition of bone loss in cancer patients which comprises administering to the patient in need thereof a therapeutically effective amount of a compound of formula III



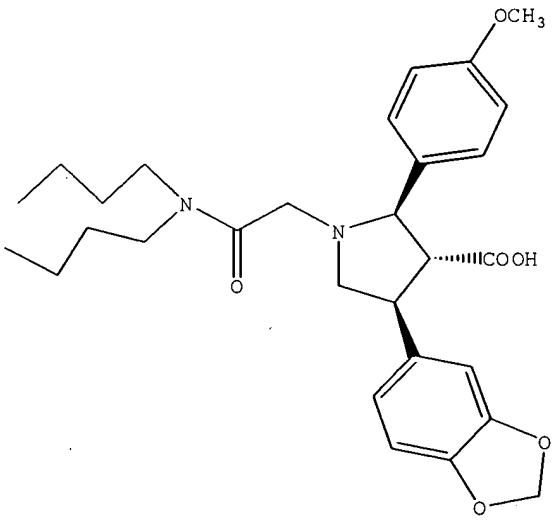
III.

147 (withdrawn): The method of Claim 146 wherein the cancer is prostate cancer and the patient is male.

148 (withdrawn): The method of Claim 146 which additionally comprises the administeration of at least one therapeutic agent which impedes net bone loss.

149 (withdrawn): The method of Claim 148 wherein therapeutic agent is a bisphosphonate.

150 (withdrawn): A method for the reduction of cancer-related pain which comprises administering to a patient in need thereof a therapeutically effective amount of a compound of formula III



III.

151 (withdrawn): The method of Claim 150 wherein the cancer is prostate cancer and the patient is male.

152 (withdrawn): The method of Claim 150 which additionally comprises the administeration of an anticancer drug.

153 (withdrawn): The method of Claim 152 wherein the anticancer drug is selected from leuprolide, goserelin, bicalutamide, nilutamide, flutamide, vitamin D, vitamin D analogues, estrogen, estrogen analogues, prednisone, hydrocortisone, ketoconazole, cyproterone acetate, and progesterone.

154 (withdrawn): A method for preventing new bone metastases in a patient which comprises administring to the patient in need thereof a therapeutically effective amount of an endothelin ET-A receptor antagonist.

155 (withdrawn): A method for inhibiting metastatic growth in a patient which comprises administring to the patient in need thereof a therapeutically effective amount of an endothelin ET-A receptor antagonist.

156 (withdrawn): A method for inhibiting bone turnover in a patient which comprises administring to the patient in need thereof a therapeutically effective amount of an endothelin ET-A receptor antagonist.

157 (withdrawn): The compound according to claim 1 wherein R_1 is aryl substituted with one substituent selected from the group consisting of methoxy, methoxyethoxy, and isopropoxyethoxy; R_2 is 1,3-benzodiox-5-yl; R_5 is methylene; and R_{12} is diarylalkyl wherein each aryl group of the diarylalkyl is substituted with methyl or ethyl.

158 (withdrawn): The compound according to claim 1 wherein R_1 is

phenyl substituted with one substituent selected from the group consisting of methoxy, methoxyethoxy, and isopropoxyethoxy; R_2 is 1,3-benzodiox-5-yl; R_5 is methylene; and R_{12} is diphenylalkyl wherein each phenyl group of the diphenylalkyl is substituted with methyl or ethyl.

159 (withdrawn): The compound according to claim 21 wherein R_1 is aryl substituted with one substituent selected from the group consisting of methoxy, methoxyethoxy, and isopropoxyethoxy; R_2 is 1,3-benzodiox-5-yl; R_5 is methylene; and R_{12} is diarylalkyl wherein each aryl group of the diarylalkyl is substituted with methyl or ethyl.

160 (withdrawn): The compound according to claim 21 wherein R_1 is phenyl substituted with one substituent selected from the group consisting of methoxy, methoxyethoxy, and isopropoxyethoxy; R_2 is 1,3-benzodiox-5-yl; R_5 is methylene; and R_{12} is diphenylalkyl wherein each phenyl group of the diphenylalkyl is substituted with methyl or ethyl.

161 (withdrawn): A compound selected from the group consisting of

trans, trans-2-(4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(N-((bis-o-tolyl)methyl)aminocarbonylmethyl)pyrrolidine-3-carboxylic acid,

trans, trans-2-(4-(2-methoxyethoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(N-(2,2-dimethyl-1-phenylpropyl)-1-aminocarbonylmethyl)pyrrolidine-3-carboxylic acid,

trans, trans-2-(4-(2-methoxyethoxy)phenyl)-4-(1,3-benzodioxol-5-yl)-1-(N-((bis-o-tolyl)methyl)amino)carbonylmethyl)pyrrolidine-3-carboxylic acid,

trans, trans-2-(4-(2-isopropoxyethoxy)phenyl)-4-(1,3-benzodioxol-5-yl)-1-(N-(2,2-dimethyl-1-phenylpropyl)-1-amino)carbonylmethyl)pyrrolidine-3-carboxylic acid,

trans, trans-2-(4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(N-(3,3-dimethyl-1-phenylbutyl)-1-amino)carbonylmethyl)pyrrolidine-3-carboxylic acid,-

trans, trans-2-(4-(2-isopropoxyethoxy)phenyl)-4-(1,3-benzodioxol-5-yl)-1-

(N-((1-o-toulyl)-1-(o-ethylphenyl)methyl)amino)carbonylmethyl)pyrrolidine-3-carboxylic acid,

trans, trans-2-(4-(2-(2-propoxy)ethoxy)phenyl)-4-(1,3-benzodioxol-5-yl)-1-(N-phenyl-N-t-butylhydrazinocarbonylmethyl)pyrrolidine-3-carboxylic acid, and

trans, trans-2-(4-(2-methoxyethoxy)phenyl)-4-(1,3-benzodioxol-5-yl)-1-(N-phenyl-N-t-butylhydrazinocarbonylmethyl)pyrrolidine-3-carboxylic acid, or a pharmaceutically acceptable salt thereof.

162 (withdrawn): A pharmaceutical composition for antagonizing endothelin comprising a therapeutically effective amount of trans,trans-2-(4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)pyrrolidine-3-carboxylic acid, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

163 (withdrawn): A pharmaceutical composition for treating cancer comprising a therapeutically effective amount of trans,trans-2-(4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)pyrrolidine-3-carboxylic acid, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

164 (withdrawn): A pharmaceutical composition for treating prostate cancer comprising a therapeutically effective amount of trans,trans-2-(4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)pyrrolidine-3-carboxylic acid, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

165 (withdrawn): A pharmaceutical composition for treating nociception comprising a therapeutically effective amount of trans,trans-2-(4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(N,N-di(n-

butyl)aminocarbonylmethyl)pyrrolidine-3-carboxylic acid, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

166 (withdrawn): A pharmaceutical composition for treating bone pain associated with bone cancer comprising a therapeutically effective amount of trans,trans-2-(4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

167 (withdrawn): A method for antagonizing endothelin comprising administering to a mammal in need of such treatment a therapeutically effective amount of trans,trans-2-(4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid, or a pharmaceutically acceptable salt thereof.

168 (withdrawn): A method for treating cancer comprising administering to a mammal in need of such treatment a therapeutically effective amount of trans,trans-2-(4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid, or a pharmaceutically acceptable salt thereof.

169 (withdrawn): A method for treating prostate cancer comprising administering to a mammal in need of such treatment a therapeutically effective amount of trans,trans-2-(4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid, or a pharmaceutically acceptable salt thereof.

170 (previously presented): A method for treating nociception comprising administering to a mammal in need of such treatment a therapeutically effective

amount of trans,trans-2-(4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid, or a pharmaceutically acceptable salt thereof.

171 (previously presented): A method for treating bone pain associated with bone cancer comprising administering to a mammal in need of such treatment a therapeutically effective amount of trans,trans-2-(4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)pyrrolidine-3-carboxylic acid, or a pharmaceutically acceptable salt thereof.

172 (withdrawn): A method for antagonizing endothelin comprising administering to a mammal in need of such treatment a pharmaceutical composition comprising a therapeutically effective amount of trans,trans-2-(4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)pyrrolidine-3-carboxylic acid, or a pharmaceutically acceptable salt thereof.

173 (withdrawn): A method for treating cancer comprising administering to a mammal in need of such treatment a pharmaceutical composition comprising a therapeutically effective amount of trans,trans-2-(4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)pyrrolidine-3-carboxylic acid, or a pharmaceutically acceptable salt thereof.

174 (withdrawn): A method for treating prostate cancer comprising administering to a mammal in need of such treatment a pharmaceutical composition comprising a therapeutically effective amount of trans,trans-2-(4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)pyrrolidine-3-carboxylic acid, or a pharmaceutically acceptable salt thereof.

175 (previously presented): A method for treating nociception comprising administering to a mammal in need of such treatment a pharmaceutical composition comprising a therapeutically effective amount of trans,trans-2-(4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)pyrrolidine-3-carboxylic acid, or a pharmaceutically acceptable salt thereof.

176 (previously presented): A method for treating bone pain associated with bone cancer comprising administering to a mammal in need of such treatment a pharmaceutical composition comprising a therapeutically effective amount of trans,trans-2-(4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid, or a pharmaceutically acceptable salt thereof.

177 (withdrawn): A pharmaceutical composition for antagonizing endothelin comprising a therapeutically effective amount of (2R,3R,4S)-(+)-2-(4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)pyrrolidine-3-carboxylic acid, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

178 (withdrawn): A pharmaceutical composition for treating cancer comprising a therapeutically effective amount of (2R,3R,4S)-(+)-2-(4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)pyrrolidine-3-carboxylic acid, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

179 (withdrawn): A pharmaceutical composition for treating prostate cancer comprising a therapeutically effective amount of (2R,3R,4S)-(+)-2-(4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(N,N-di(n-

butyl)aminocarbonylmethyl)pyrrolidine-3-carboxylic acid, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

180 (withdrawn): A pharmaceutical composition for treating nociception comprising a therapeutically effective amount of (2R,3R,4S)-(+)-2-(4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)pyrrolidine-3-carboxylic acid, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

181 (withdrawn): A pharmaceutical composition for treating bone pain associated with bone cancer comprising a therapeutically effective amount of (2R,3R,4S)-(+)-2-(4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

182 (withdrawn): A method for antagonizing endothelin comprising administering to a mammal in need of such treatment a therapeutically effective amount of (2R,3R,4S)-(+)-2-(4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid, or a pharmaceutically acceptable salt thereof.

183 (withdrawn): A method for treating cancer comprising administering to a mammal in need of such treatment a therapeutically effective amount of (2R,3R,4S)-(+)-2-(4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid, or a pharmaceutically acceptable salt thereof.

184 (withdrawn): A method for treating prostate cancer comprising administering to a mammal in need of such treatment a therapeutically effective

amount of (2R,3R,4S)-(+)-2-(4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid, or a pharmaceutically acceptable salt thereof.

185 (previously presented): A method for treating nociception comprising administering to a mammal in need of such treatment a therapeutically effective amount of (2R,3R,4S)-(+)-2-(4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid, or a pharmaceutically acceptable salt thereof.

186 (previously presented): A method for treating bone pain associated with bone cancer comprising administering to a mammal in need of such treatment a therapeutically effective amount of (2R,3R,4S)-(+)-2-(4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)pyrrolidine-3-carboxylic acid, or a pharmaceutically acceptable salt thereof.

187 (withdrawn): A method for antagonizing endothelin comprising administering to a mammal in need of such treatment a pharmaceutical composition comprising a therapeutically effective amount of (2R,3R,4S)-(+)-2-(4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)pyrrolidine-3-carboxylic acid, or a pharmaceutically acceptable salt thereof.

188 (withdrawn): A method for treating cancer comprising administering to a mammal in need of such treatment a pharmaceutical composition comprising a therapeutically effective amount of (2R,3R,4S)-(+)-2-(4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)pyrrolidine-3-carboxylic acid, or a pharmaceutically acceptable salt thereof.

189 (withdrawn): A method for treating prostate cancer comprising administering to a mammal in need of such treatment a pharmaceutical composition comprising a therapeutically effective amount of (2R,3R,4S)-(+)-2-(4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)pyrrolidine-3-carboxylic acid, or a pharmaceutically acceptable salt thereof.

190 (previously presented): A method for treating nociception comprising administering to a mammal in need of such treatment a pharmaceutical composition comprising a therapeutically effective amount of (2R,3R,4S)-(+)-2-(4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)pyrrolidine-3-carboxylic acid, or a pharmaceutically acceptable salt thereof.

191 (previously presented): A method for treating bone pain associated with bone cancer comprising administering to a mammal in need of such treatment a pharmaceutical composition comprising a therapeutically effective amount of (2R,3R,4S)-(+)-2-(4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid, or a pharmaceutically acceptable salt thereof.